



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/660,798 Confirmation No.: 6154
Applicant : REDMOND, et al.
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Examiner : James D. Anderson
Docket No. : 1194-282
Customer No. : 6449

RULE 132 DECLARATION OF DR. H. PAUL REDMOND

I, H. Paul Redmond, declare as follows:

1. I am the same H. Paul Redmond named as one of the inventors in the above-referenced application.
2. I am Professor of Surgery, Head of Department of Surgery at the Cork University Hospital, Cork Ireland and a member of the Royal College of Surgeons of Ireland. A copy of my curriculum vitae is attached hereto as Exhibit A.
3. I am familiar with the subject patent application, including the currently pending claims and the amended claims to be submitted with this Declaration. I am also familiar with the references cited in the July 13, 2006 Office Action, including those of Carter, et al., Monson (WO 92/00743), and Morrissey, et al. (U.S. Pat. No. 6,303,596).
4. I understand that amended claim 1 to be submitted with this Declaration recites a method of inhibiting tumor growth in a cancer patient comprising administering to said patient a combination therapy comprising effective amounts of 5-Fluorouracil (5-FU) and a methylol transfer agent, said methylol transfer agent being capable of substantially enhancing antineoplastic effects of said 5-FU, substantially reducing toxic side effects of said 5-FU, or a combination thereof, wherein said methylol transfer agent has a substantial effect on activity of said 5-FU, said substantial effect being selected from the group consisting of substantially enhancing antineoplastic effects of said 5-FU, substantially reducing toxic side effects of said

5-FU, and a combination thereof, wherein the methylol transfer agent is taurolidine, tauraltam, or a mixture thereof.

5. I understand that amended claim 10 to be submitted with this Declaration recites a combination comprising 5-FU and a methylol transfer agent in effective amounts for simultaneous, separate or sequential use for inhibiting tumor growth in a cancer patient, said methylol transfer agent being capable of substantially enhancing antineoplastic effects of said 5-FU, substantially reducing toxic side effects of said 5-FU, or a combination thereof, wherein said methylol transfer agent has a substantial effect on activity of said 5-FU, said substantial effect being selected from the group consisting of substantially enhancing antineoplastic effects of said 5-FU, substantially reducing toxic side effects of said 5-FU, and a combination thereof, wherein the methylol transfer agent is taurolidine, tauraltam, or a mixture thereof.

6. 5-Fluorouracil (5-FU) is an antineoplastic drug with clinical activity in a variety of tumors, such as cancers of the colon and rectum, head and neck, liver, breast, and pancreas. One problem with 5-FU is its extreme toxicity. Since 5-FU targets rapidly dividing cells, the primary toxic side effects are on bone marrow, intestinal mucousa and oral mucousa. Thus, leukocyte and platelet count decreases substantially after administration. Other side effects include stomatitis, diarrhea, nausea and vomiting. Neurological side effects include somnolence and ataxia. Other side effects include chest pain, myocardial necrosis and ischemia. Inflammatory reactions such as acute and chronic conjunctivitis leading to tear duct stenosis and ectropion also occur.

7. I have conducted studies in connection with taurolidine and 5-FU, and have surprisingly found that methylol transfer agents such as taurolidine and taurultam substantially enhance or augment the antineoplastic effects of 5-FU in a combination therapy for inhibiting tumor metastases and treating cancer in patients. Such methylol transfer agents also substantially reduce the toxic side effects of 5-FU.

8. My studies have demonstrated that taurolidine in combination with 5-FU is more effective than 5-FU alone, thus suggesting that the 5-FU dosage in the combination could be reduced, which could in turn reduce the frequency and/or severity of the adverse effects of 5-FU, without diminishing its efficacy.

9. Attached as Exhibit B is a set of graphical data demonstrating the effects of taurolidine and 5-FU, individually and in combination, on proliferation of SW 480 (colo-rectal tumor cells). Taurolidine has proven anti-neoplastic effects and appears to be directly cytotoxic to tumor cells. From the data, it can be seen that taurolidine augments the action of 5-FU in human colo-rectal tumor cells and that the combination of taurolidine and 5-FU exhibits a surprising synergistic effect.

10. In my opinion, the results obtained, including the synergistic effect reflected therein, are surprising and would not be expected to be achieved based on the teachings in the various references cited in the July 13, 2006 Office Action. Specifically, one simply would not expect the combination therapy recited in amended claim 1 to achieve the success exhibited in the study. I believe, therefore, that the present invention, as demonstrated through the attached information, provides surprising and unexpected advantages over previously known anti-cancer therapies and is therefore inventive over the prior art cited in the July 13, 2006 Office Action.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/19/06

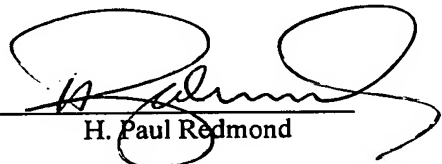
Signed: 
H. Paul Redmond

EXHIBIT A

CURRICULUM VITAE

HENRY PAUL REDMOND

B.Sc. (Anat), M.B., B.Ch., B.A.O., L.R.C.P.& S.I., M. Ch., F.R.C.S.I.(gen)

PERSONAL INFORMATION

Name: Henry Paul Redmond

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Cork University Hospital,
Wilton,
Cork.
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Nationality: Irish

Birthdate: August 13th, 1959

MEDICAL EDUCATION

Undergraduate:

Medical School: Royal College of Surgeons in Ireland
Date of Entry: October 1977
Date of Graduation: June 1983
Degrees: M.B., B.Ch., B.A.O., L.R.C.P.I. &
L.R.C.S.I. (Hons)

Postgraduate:

1984-1986	B.Sc. (Anatomy)
1985	Primary Fellowship in Surgery
1987	Final Fellowship in Surgery
1992	M. Ch, N.U.I.
1995	Intercollegiate Fellowship in General Surgery

POST GRADUATE ACADEMIC DISTINCTIONS

- First place and Silver medal Primary Fellowship of Royal College of Surgeons in Ireland, 1985.
- First Class Honours and Joint First Place B.Sc. Anatomy, UCD, 1985
- First Place Final Fellowship in General Surgery of Royal College of Surgeons in Ireland 1987.
- International Fogarty Scholarship Award, 1989.
- International Leucocyte Biology Research Travel Award, 1990.
- Harry M. Vars Research Award, (co-author), 1991.
- NIH research award, 1991.
- Ethicon Foundation Travel award, 1992.
- R.C.S.I Council prize for research, 1992
- Sheppard prize for scientific research, Beaumont hospital, 1992.
- European Society of Surgical Research, Young Investigator award (senior author), 1992.
- R. A. M. I. Registrars prize in Surgery, (senior author), 1992.
- R.C.S.I. Research award, (senior author), 1992.
- Sir Peter Freyer Research Award, (co-author), 1992.
- Ethicon Foundation Travel award, 1993.
- Patey prize finalist, January 1993.
- European Community Fellowship in Oncology, 1993.
- R. A. M. I. Registrars prize in Surgery, (co-author), 1993.
- Sheppard prize for scientific research, RCSI, (senior author) 1993.
- Intensive Care Society of Ireland award for research, (co-author) 1993.
- Presidential medal, Irish Society of Gastroenterology, (co-author) 1993
- Association of Academic Surgery, Residents research award, USA, (co-author) 1993.
- Ethicon Foundation Travel award, 1994.
- Biological Society Research award, RCSI (senior author), 1993.
- Winner, Royal Society of Medicine Coloproctology Travelling Scholarship, 1993.
- Sheppard prize for scientific research, Beaumont Hospital, (senior author) 1994.
- Irish Association for Cancer Research, research award, (senior author), 1994.
- Patey prize for research, Surgical Research Society, (co-author), 1995.
- Royal College of Surgeons in Ireland, Council prize, (senior author) 1995.
- Gussie Mehigan scholarship winner 1995.
- Sheppard prize for scientific research, research award, (senior author), 1995.
- Surgical Infection Society of Europe, award for best research, 1995.
- Irish Society of Gastroenterology, first place for research, 1995.
- Irish Society of Gastroenterology, second place for research, 1995.

MEMBERSHIP OF LEARNED SOCIETIES

- Fellow of Royal Academy of Medicine in Ireland.
- Member of Surgical and Academic Research Society of Great Britain and Ireland.
- Member of Surgical Infection Society of North America.
- Member of American Society for Parenteral and Enteral Nutrition Member of Surgical Infection Society of Europe.
- Member of the MPS.
- Fellow of Royal College of Surgeons in Ireland.
- Member International Leucocyte Biology Society.
- Member of Association of Academic Surgery.
- Member of the Irish Society of Gastroenterology.
- Member of the Royal Society of Medicine.
- Member of Irish Society of Coloproctology.
- Member of Association of Endoscopic Surgeons of Great Britain and Ireland.
- Member of Society of Surgical Oncology.
- Member of American Academy of Sciences.
- Member of the Surgical Infection Society of Europe,
- Member of the Society of Endoscopic Surgeons of Great Britain and Ireland
- Member of the Shock Society
- Member of the Society of University Surgeons
- Member of the American Society of Clinical Oncology
- Member of the European Society of Surgical Research
- Member of the European Society of Surgery
- Member of the Society of Coloproctology of Great Britain and Ireland
- Member of the Association of Surgeons of Great Britain and Ireland

POSITIONS OF AUTHORITY ON COMMITTEES

- Chairman, National Cancer Forum of Ireland
- Regional Director of Cancer Services for the Southern Health Board
- Scientific Director for the Association of Surgeons of Great Britain and Ireland
- Membership Director for the Society of Academic and Research Surgery
- Member of Editorial Board - Sepsis
- Council Member of the Royal College of Surgeons in Ireland

PROFESSIONAL EXPERIENCE

RESEARCH POSITION

1989-1991

Research Fellow University of Pennsylvania,
Philadelphia, USA.

POST-FELLOWSHIP SURGICAL TRAINING AT REGISTRAR / SENIOR REGISTRAR LEVEL.

1991-1992

Surgical Registrar, Beaumont Hospital, Dublin

1992-1993

Senior Registrar, Waterford Regional Hospital.

1993-1994

Senior Registrar, Beaumont Hospital.

1994-1995

Lecturer in Surgery, Royal College of Surgeons in
Ireland and Beaumont Hospital.

1996-1997

Senior Lecturer/Consultant Surgeon, Royal
College of Surgeons in Ireland and Beaumont Hospital.

1997 - present

Professor/Head of Department of Surgery,
University College Cork and Cork University Hospital.

BIBLIOGRAPHY

PEER REVIEWED JOURNAL ARTICLES

Redmond HP and Lane BE. A 10 year review of gunshot injuries in a Dublin teaching Hospital. *Ir J Med Sci* 154: 395, 1985

Redmond HP, Fitzgerald DE, Donohue J. A non-invasive method in the assessment of arterio-venous fistulae for uraemia. *Eur J Vasc Surg* 311:4 1987

Redmond HP, Broe PJ, Bouchier-Hayes D. Vascular complications of varicose vein surgery in Ireland. *Phlebology* 3: 251, 1988

Redmond HP, Daly NN, Gorey TF. An approach to selective conservative management of liver injuries. *Ir Med J* 81: 14, 1988

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Redmond HP, Leon P, Hofmann KP, Goldfine J, Shou J, Daly JM. Alteration in macrophage function following surgical trauma. *Surg Forum II*: 54:6, 1990

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Shou J, Lieberman MD, Hofmann K, Redmond HP, Leon P, Davies Helen, Daly JM. Dietary manipulation of methotrexate-induced enterocolitis. JPEN 1991; 15:307, 1991.

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Wang J, Redmond HP, Watson RWG, et al. Mechanisms involved in the induction of human endothelial cell necrosis. *Cell Immunol* 168: 91 1996

Watson RW, Redmond HP, Wang JH, Bouchier-Hayes DJ. Bacterial ingestion, tumour necrosis factor-alpha, and heat induce programmed cell death in active neutrophils. Shock. 5(1):47 1996.

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Redmond HP, Wang JH, Bouchier-Hayes DJ. Taurine attenuates nitric oxide and reactive oxygen intermediate-dependent hepatocyte injury. Arch Surg. 131(12): 1280 1996.

Hill ADK, Redmond HP, Bouchier-Hayes D. Granulocyte-macrophage colony-stimulating factor inhibits tumour growth during the postoperative period. Surgery.; 119(2):178 1996.

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Redmond HP, Wang JH, Bouchier-Hayes D. Taurine attenuates nitric oxide and reactive oxygen intermediate-dependent hepatocyte injury. Arch Surg 131(12):1280, 1996

Neary P, Houghton T, Redmond HP, Watson RWG, Bouchier-Hayes D. Carcinoid Syndrome - a review. Dis Colon Rectum 40:349 1996

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